Food and Drug Administration
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MEMORANDUM

DATE: August 28, 2002
FROM: Melanie Hartsough, Ph.D., DTP

THROUGH: Blair Fraser, Ph.D., DTP
Barry Cherney, Ph.D., DTP
Amy Rosenberg, M.D., DTP

SUBJECT: BLA STN 125058/0 (reference: BB-IND 7334)
CMC Product Review

PRODUCT: Aldurazyme (laronidase; recombinant human a-L-iduronidase or rhIDU)
PROPOSED USE: To treat patients with late-stage mucopolysaccharidosis I

ADMINISTRATION:
Company: Biomarin Pharmaceutical, Inc
Responsible Head: Matt Patterson, Vice-president, Regulatory and Government Affairs
Phone Number: 415-884-6720

TO: File and Sponsor

A. INTRODUCTRION

I 1. Summary

Aldurazyme, human, recombinant I-L-iduronidase, is indicated for long-term enzyme replacement therapy in patients with confirmed Mucopolysaccharidosis I. The full-length, glycosylated a-L-iduronidase protein is produced by a Chinese Hamster Ovary cell line that has been stably transfected with the a-L-iduronidase cDNA coding region. The protein is secreted into the cell culture media and then purified from the supernatant by a series of ----------. The purified protein is formulated with polysorbate 80 in sodium chloride and sodium phosphate buffer and is supplied as a liquid concentrate for intravenous infusion at a dose of 100 units per kilogram of patient body weight.

Alpha- L-iduronidase is an enzyme that is essential for the catabolism of mucopolysaccarides or glycosaminoglycans (GAGs) heparan sulfate and dermatan sulfate. A deficiency or absence of this enzyme results in an accumulation of dermatan sulfate and heparin sulfate in the body. This condition is an autosomal recessive lysosomal storage disease known as Mucopolysaccharidosis I. In Mucopolysaccharidosis I patients, some of the excess GAGs are excreted in the urine, but an accumulation of these substrates, to damaging levels, in lysosomes occurs in numerous tissues, subsequently leading to

such abnormalities as gargoyl-like facial features, dwarfism, kyphosis, limited joint movement, abnormalities of the heart, spleen, and liver, clouding of the cornea and learning disorders. The disease ranges in conditions of rapidly progressive Hurler's syndrome (MPS type I H, severe) with a life expectancy of approximately 10 years, to slowly progressive Schei syndrome (MPS type I S, mild) with normal life expectancy. Phenotypes between the two extremes are characterized as Hurler/Schei syndrome (MPS type I H/S, intermediate).

I 2. Review Comments

1. Please provide information that confirms that the assays used for release testing of drug substance provide an assurance that all ---------- bonds have been correctly formed.

2. For formulated drug substance, please tighten your specifications ----------

3. For final container drug product, please tighten your specifications for activity, osmolality and polysorbate 80 to a maximum of mean +/- 3 S.D.

4. Please be aware that at the time of licensure, expiration dating will be granted based upon real time data that has been submitted for three formulated drug substance lots and three final container drug product lots that use the identical container.

5. Please place one drug product lot from each manufacturer on stability at 2-8 °C annually.

6. Aggregation of product could enhance immune responses, specifically neutralizing antibody, which may limit the response to therapy, whereas highly deaggregated product may induce immune tolerance. Mindful of this immunogenicity potential, please justify ----------

7. Please submit copies of the certificates of analysis for the conformance batches of drug substance and conformance lots of drug product.

8. With regard to step yields in the purification process, in ---------- and/ or justify the action limits for the ----------

<u>Items that will be addressed during inspection:</u>

1. Please provide the photostability data acquired in the degradation study.

2. Please provide the SOP for setting specifications.

3. Please provide information on reference requalification.

4. Please submit the bioburden data for the stability study performed on the process intermediates.

5. Please submit copies of the certificates of analysis for the conformance batches of drug substance and conformance lots of drug product.

B. BODY OF DATA

S. DRUG SUBSTANCE

The rhIDU formulated bulk drug substance is ----------

S 1. General Information

S 1.1 Nomenclature

- Interational non-proprietary name (INN) = Laronidase
- United States Adopted Name (USAN) = Laronidase
- Trivial name = recombinant human a-L-iduronidase
- Trade name = Aldurazyme™

S 1.2 Structure

The secreted, recombinant human a-L-iduronidase protein is also referred to as the precursor protein. The predicted, full length protein undergoes signal peptide cleavage of the first 25 amino acids to produce the precursor protein, which contains 628 amino acids with the N-terminus being alanine-26. Enzyme that is not secreted is further processed in the lysosome and is known as the processed form.
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There are six N-linked oligosaccharide modification sites utilized in the recombinant protein. The oligosaccharides occupying the third and sixth sites have been shown to contain the bis-mannose-6-phosphate oligomannose$_7$ oligosaccharide required for uptake into cells

S 1.3 General Properties

- MW= The recombinant, precursor protein has an expected molecular weight of 70.1 kDa, but due to glycosylation has an apparent molecular weight of 83 kDa by ----------

- Sequence= Sequencing data for the human a-L-iduronidase protein is in Appendix IIC-1

S 2. Manufacture

S 2.1 Manufacturer(s)

BioMarin
Pharmaceutical Inc.
46 Galli Drive
Novato, CA 94949, USA.

S 2.2 Description of Manufacturing Process and Process Controls

A. Raw Materials

Material	**Source**	**Origin**	**Purpose**
	bovine	Mexico, U.S., Canada	
	porcine	U.S., Canada	
Polysorbate 80	plant	-------	
	plant	-------	
	bovine and porcine after ---------- ---------- ----------	U.S	

**Note: Certificate of Analyses and descriptions of viral testing were provided where appropriate (sections IIV 2.2 and 2.3)*

**As of 8/02, BSE has not been identified in Mexico; Mexico is considered BSE free (as per email communication from David Asher).*

- Cell culture raw materials are listed in Tables IIC-11
- Release testing of raw materials are listed in Tables IIC-11 and IIC-17

B. Cell substrate/Host Cell/Expression Vector System

(1) Host cells

The host cell is a ------Chinese hamster ovary cell, designated ---------- originating ----------. An aliquot of this cell line was transferred from ---------- to

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S 4.2 Analytical Procedures

All the analytical methods used for the bulk drug substance are listed and described in the Method Validation Package in Section R2.

S 4.3 Validation of Analytical Procedures

All the analytical methods used for the bulk drug substance have been validated Refer to the Method Validation Package in Section R2.

S 4.4 Batch Analyses

Batch Number	**Material Use**
	Pre-clinical, Clinical
	Pre-clinical, Clinical
	Pre-clinical, Clinical
	Pre-clinical, Clinical
	Pre-clinical, Clinical, Reference Standard, Proposed Commercial Use
	Clinical, Reference Standard, Proposed Commercial Use
	Clinical, Reference Standard, Proposed Commercial Use
	Clinical, Proposed Commercial Use
	Clinical, Proposed Commercial Use
	Clinical, Proposed Commercial Use
	Clinical, Proposed Commercial Use
	Clinical, Proposed Commercial Use

Formulated Bulk Drug Substance Batch Analysis Results

Test	**Specifications**												

S 4.5 Justification of Specification (see Table on the next page)

All methods used in the release of Aldurazyme were validated in accordance with the International Conference on Harmonization Guidelines on the validation of analytical procedures. Biomarin stated that the specifications were established based on a minimum of three standard deviations about the mean for the determined intermediate precision of the method.

Reviewer's Comment:

Biomarin has assigned specifications for ----------. These specifications either need to be changed or further justified.

Formulated Bulk Drug Substance Release Testing Summary for 12 lots

Test	Specifications	Intermediate Precision	Mean	SD	Mean +/- 3 S.D.	Relative S.D. (% error)	Range

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S 5. Reference Standards or Materials

Three lots (----------) were manufactured according to the commercial production process and are intended to be used for clinical and commercial requirements[

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S.5.1 Qualification and Comparability of Reference Standard

Qualification of rhIDU reference standards (Table IIC-44)

Test	**Specifications**	**Previous Reference** ----------	**Current Reference** ----------

S.5.2 Reference Material Stability

The stability of reference lot ----------, stored at ----------C, will be monitored by the following assays:----------
Stability data have been provided for - months. *There are no significant changes observed; the material is stable for at least -- months when stored at ----------°C.*

S.5.3 Reference Material History

Multiple lots of rhIDU have been used as controls during development. Lots ---------- ---- were used as controls to release Phase 1/2 clinical product. These lots were manufactured by the --- L production process and were specifically used as controls for ----------. These lots have been exhausted

S 6. Container Closure System

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Stability of formulated bulk drug substance @ -----C

P. DRUG PRODUCT

P 1. Description and Composition of the Drug Product

Aldurazyme is a solution that is administered by infusion once a week. Each vial contains 5.3 mL of solution, which allows a 5.0 mL extraction. For administration to patients, Aldurazyme is diluted with 0.9% sodium chloride to a volume of between 100 mL and 250 mL. Whenever possible, the volume is adjusted to meet the fluid requirements of the patient. Patients receive Aldurazyme at a nominal dose of 100 units/kg (approximately 0.58 mg/kg).

Composition of Aldurazyme Drug Product (Table IIA-1)

Ingredient	Concentration	Composition per vial	Function	Reference standard
rhIDU	100 units/ml	2.90 mg	Active ingredient	In house standard
Sodium Chloride	150 mM	43.9 mg	Tonicity Modifier	USP/EP
Sodium Phosphate, monobasic monohydrate	92 mM	63.5 mg	Buffer	USP/EP
Sodium Phosphate, dibasic, heptahydrate	8 mM	10.7 mg	Buffer	USP/EP
Poysorbate 80	10 µg/ml	0.05 mg	Stabilizer	NF/EP
Water for injection		5 ml		USP/EP

P 2. Pharmaceutical Development

P 2.1 Components of the Drug Product

P 2.1.1 Drug Substance

P 2.1.2 Excipients

Ingredient	Function	Reference to standard
Sodium Chloride	Tonicity Modifier	USP/EP
Sodium phosphate, monobasic, monohydrate	Buffer	USP/EP
Sodium phosphate, dibasic, heptahydrate	Buffer	USP/EP
Polysorbate 80	Stabilizer	NF/EP
Water for injection	solvent	USP/EP

P 2.2 Drug Product

P 2.2.1 Formulation Development

The original Phase 1/2 clinical study formulation was identical to the commercial

formulation with the exception that polysorbate 80 was added as a stabilizer (reduce precipitates) in the commercial formulation.

The use of the commercial formulation was initiated in August of 2000 during the extension portion of the Phase 1/2clinical study entitled “Enzyme Replacement Therapy in the Treatment of Mucopolysaccharidosis I” (Protocol number BIO7500–001) as a separate protocol entitled “A Cross-Over Sub-Study for Safety and Enzyme Levels of Aldura zyme, Transfer of Patients from Carson Street Product to Galli Drive Product.” The commercial formulation was used in the Phase 3 clinical study entitled “A Randomized, Double-Blind, Placebo-Controlled, Multinational, Clinical Study of Recombinant Human Alpha-L-iduronidase (ALID-003-99)” and will be used for commercial material.

One lot of Aldurazyme placebo was made for the Phase 3 clinical study. The manufacturing of the Aldurazyme placebo was performed in the Galli Manufacturing Facility in accordance with current good manufacturing practices. The procedure consists of making the final formulation buffer with the addition of polysorbate 80 to a concentration of 10 µg/mL. The Aldurazyme placebo was shipped to Genzyme ----------
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Two modifications have been implemented in the formulation that have not significantly changed the product administration. These include:

1. The activity of the product used in the early pre-clinical studies and the Phase 1/2 clinical study was defined as 125,000 units/mL. Due to subsequent optimization and validation of the product activity assay in June 2000, the original product activity of 125,000 units/mL was redefined as 100 units/mL. This was due to a re-definition of the activity unit and does not reflect a change in the absolute product activity.

2. The concentration assay was also optimized. The protein concentration in the early pre-clinical studies and the Phase 1/2 clinical study was described as approximately 0.5 mg/mL, as determined using the [

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P 2.2.2 Overages

P 2.2.3 Physicochemical and Biological Properties

P 2.3 Manufacturing Process Development

During development the drug product manufacturing process (filling of rhIDU formulated bulk drug substance into vials) was moved to Genzyme Corporation and ---------- to accommodate increases in production scale.

P 2.4 Container Closure System

The drug product container was changed from a ----------vial to a Type 1 glass vial and the ---------- stopper was replaced with a ----------butyl stopper. Both changes were made to enhance compatibility between product and the container-closure components.

P 2.5 Microbiological Attributes—Not Applicable

P 2.6 Compatibility

P 3. Manufacture

P 3.1 Manufacturer(s)

Genzyme Corporation (Allston Landing facility), located in Allston, Massachusetts, USA or ---------- . The floor plans are located in Appendix IIB-1 and Appendix IIB-2.

P 3.2 Batch Formula

The Manufacturing Formula is the same as the Clinical Trial Formula used in the Phase 3 clinical study and is the same at ---------- and Genzyme. The formula is described in Section P1 the table entitled "Composition of Aldurazyme Drug Product (Table IIA-1)"

P 3.3 Description of Manufacturing Process and Process Controls

The Drug Product is prepared by the sterile filtration and filling of recombinant human a L-iduronidase formulated bulk drug substance into vials. These vials are stoppered, capped, and labeled, at which point the product is referred to as Aldurazyme. (see Table IIB-2 for details)

P 3.4 Controls of Critical Steps and Intermediates

Genzyme: In-process testing is performed during the processing of each lot of Aldurazyme from formulated bulk drug substance to drug product at Genzyme. Methods for the determination of identity ----------, and sterility (21 CFR 610.12 USP/EP) are performed at appropriate stages of the filling operations.

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Reviewers comment:

---------- is asking for exemption from sterility testing due to the nature of the manufacturing. The filling process involves [

]. DMPQ will decide whether the exemption is approvable.

P 3.5 Process Validation and/or Evaluation

The Aldurazyme filling process has been validated through performance qualification of the filling equipment with respect to delivery volume, yield, stopper placement, and particulate generation (refer to Section IIB 3.1.2 and Section IIB 3.2.2).

•DMPQ will determine the adequacy of the Process Validation

P 4. Control of Excipients

BioMarin uses qualified suppliers who provide materials compliant with USP/EP monographs. With the exception of WFI manufactured at BioMarin, the following procedure is used to release these excipient

materials to manufacturing: materials are received by Quality Control, placed in quarantine status and subjected to identity tests and review of suppliers' certificates of analysis and upon confirmation of meeting specifications they are released for use. WFI manufactured at BioMarin is tested to both USP and EP compendial requirements.

P 4.1 Specifications

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P 4.2 Analytical Procedures

Descriptions of all of the analytical method used to determine ---------- can be found in R2. Method Validation Package.

P 4.3 Validation of Analytical Procedures

Validation information for the ---------- method can be found R2. Method Validation Package.

P 4.4 Justification of Specifications— See Below

P 4.5 Excipients of Human or Animal Origin— None

P 4.6 Novel Excipients— None

P 5. Control of Drug Product

P 5.1 Specification(s)

Test	**Specifications**
Sterility (USP/EP 21CFR 610.12)	
Volume in Container (USP)	
pH (USP)	
Polysorbate 80	

P 5.2 Analytical Procedures

Descriptions of all of the analytical methods used to evaluate the drug product can be found in R2. Method Validation Package.

P 5.3 Validation of Analytical Procedures

The methods used to evaluate the drug product have been validated. Those assays that have been validated for the drug product can be found in R2. Method Validation Package.

P 5.4 Batch Analyses (see next page)

Drug Product Manufacturing Summary

Drug Product lot number	**Formulated bulk drug substance lot number**	**Date of manufacture**	**Fill location**	**Material use**
		April 5, 2000	Genzyme	Pre-clinical
		June 16, 2000	Genzyme	Pre-clinical
		June 22, 2000	Genzyme	Pre-clinical, Clinical
		August 24, 2000	Genzyme	Clinical
		October 5, 2000	Genzyme	Clinical
		October 26,2000	Genzyme	Clinical
		December 28, 2000	Genzyme	Clinical
		March 9, 2001	----------	Clinical, Validation, Proposed Commercial
		March 22, 2001	Genzyme	Clinical, Validation, Proposed Commercial
		June 21, 2001	Genzyme	Clinical, Validation, Proposed Commercial
		July 19, 2001	Genzyme	Clinical, Validation, Proposed Commercial
		August 9, 2001	----------	Clinical, Validation, Proposed Commercial
		August 13, 2001	----------	Clinical, Validation, Proposed Commercial

Drug Product Batch Analysis Results

Test	**Specifications**													
Sterility		Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Volume in container		5.2	5.2	5.2	5.4	5.2	5.3	5.2	5.2	5.2	5.2	5.2	5.2	5.2
pH		5.5	5.6	5.6	5.5	5.5	5.5	5.5	5.5	5.6	5.5	5.5	5.6	5.6
Polysorbate 80		9	8	9	9	10	8	10	8	7	7	8	6	8

P 5.5 Characterization of Impurities

P 5.6 Justification of Specification(s)

All methods were validated in accordance with ICH guidelines on the validation of analytical procedures. The sponsor states that specifications were established based on a minimum of 3 standard deviations about the mean.

Drug Product Release Testing Summary for 13 lots

Test	**Specifications**	**Mean**	**SD**	**Mean +/- 3 S.D.**	**Relative S.D. (% error)**	**Range**

Reviewer's Comment

Three assays (----------) have specifications that are outside of the mean +/- 3 S.D. The sponsor needs to justify these specifications.

P 6. Reference Standards or Materials

There is only one reference standard that is used for both the drug substance and the drug product. This is lot ---------- is a pool of 500 ml of each formulated bulk drug substance lots ---------- that is stored in ----------C. These lots were manufactured according to the commercial production process and are intended to be used for clinical and commercial requirements. Each lot passed release specifications.

P 7. Container Closure System

The drug product is stored in a 5 cc ---------- glass vial with a 20 mm opening that meets USP/EP specifications for Type I glass (----------) The vial is manufactured from borosilicate tubing glass and is ---------- to strengthen the glass and limit potential protein adsorption. The closure for the vial is a 20 mm gray butyl ---------- serum style stopper made from the ---------- rubber formulation (---------- ---------- It meets UPS/EP specifications. The stoppers are siliconized (----------) for machinability prior to sterilization. The stoppered vial is crimped with a 20 mm ----------flip-off six bridge aluminum seal with a plastic button made of ---------- The current stopper replaced a bromobutyl rubber stopper that was used during clinical development. This change was based on the vendor's recommendation for known interaction between bromobutyl stoppers and phosphate solutions. This change in stopper composition was incorporated at both fill/finish facilities starting with the first process qualification fills of formulated bulk drug substance (lot ----------).

P 8. Stability

P 8.1 Stability Summary and Conclusion

P 8.1.1 Stability of Drug Product in Vials

Real-time and accelerated stability data are provided for -------- lots of Aldurazyme drug product stored at 2–8°C. The ---------- most recent drug product lots were produced from formulated bulk drug substance lots using the proposed commercial manufacturing process. The first -------- drug product lots on stability were packaged with a --------butyl stopper, while the next ----- lots were packaged with a --------butyl stopper, which is the proposed commercial stopper (see summary below)

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P 8.1.2 Stability of Drug Product Diluted in Infusion Bags

For administration to patients, Aldurazyme is diluted with 0.9% sodium chloride containing 0.1% human serum albumin to a volume of between 100 mL and 250 mL in an infusion bag. A study was performed to examine the stability of the infusion preparation when stored at ----------) for up to ---- hours, and refrigerated (2–8°C) for up to --- hours. The range of dilutions evaluated was between --------- units/mL. All patients receive 100 units per kilogram of body weight. These stability studies were performed to bracket the possible clinical range of dilutions of Aldurazyme.

The lowest concentration infusion configuration was prepared by adding 0.1% human serum albumin to a 100 mL bag of 0.9% sodium chloride for injection. After mixing and equilibrating for a minimum of --- minutes, --- mL of Aldurazyme derived from lot ---------- were added to the bag and mixed. The highest concentration infusion configuration was prepared by adding 0.1% human serum albumin to a 250 mL bag of 0.9% sodium chloride for injection. After mixing and equilibrating for a minimum of ---- minutes, ------ mL of Aldurazyme were added to the bag and mixed. Separate bags were prepared for each storage condition and samples were withdrawn directly from the bag at each time point through ----------

Stability was assessed by the ---------- test. Samples were stored under refrigerated and ---------- conditions. Assessment was for a ----hour duration at ----------hour time points for samples stored at 2–8°C, and a ----hour duration at ----------hour time points for samples stored at room temperature.

Reviewer's Comment

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P 8.2 Post-approval Stability Protocol and Stability Commitment

- The drug product 2–8°C studies will continue for --- months.

- ------- drug product ---- will be placed on stability at 2–8°C annually in accordance with the protocol defined above. Vials will be stored in the inverted orientation only.

Reviewer's Comment

One drug product lot filled at Genzyme and one filled at ---------- should be placed on the stability protocol each year.

P 8.3 Stability Data

- The stability data for ---------- vials stored at 2-8°, ----------C are found in Tables IIF-21 to IIF-34.

- The stability data for the infusion bag study is found in Tables IIF-35 and IIF-36.

A. APPENDICES

A 1. Facilities and Equipment

DMPQ will determine adequacy

A 2. Adventitious Agents Safety Evaluation

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R. REGIONAL INFORMATION

R1 Executed Batch Records (USA only)

•Appendix IIC-116, IIC-117 and IIC-118 contain a BioMarin batch record for the manufacture of the drug substance (lot ----------)

•Appendix IIB-3 contains a Genzyme batch record for drug product manufacture

•Appendix IIB-4 contains a ---------- batch record for drug product manufacture

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C. KEY LITERATURE REFERENCES

Bam NB, Cleland JL, Yang J, Manning MC, Carpenter JF, Kelley RF et al. Tween Protects Recombinant Human Growth Hormone Against Agitation-Induced Damage Via Hydrophobic Interactions. J Pharm Sci 1998; 87(12):1554-1559.

Hague C, Masada RI, Starr C. Structural Determination of Oligosaccharides From Recombinant Iduronidase Released With Peptide N-Glycanase F Using Fluorophore- Assisted Carbohydrate Electrophoresis. Electrophoresis 1998; 19(15):2612-2620.

Huang MT, Gorman CM. Intervening Sequences Increase Efficiency of RNA 3' Processing and Accumulation of Cytoplasmic RNA. Nucleic Acids Res 1990; 18(4):937-947.

Kakkis ED, Matynia A, Jonas AJ, Neufeld EF. Overexpression of the Human Lysosomal Enzyme a-L-Iduronidase In Chinese Hamster Ovary Cells. Protein Expr Purif 1994; 5:225-232.

Kakkis ED, Neufeld EF. The Mucopolysaccharidoses. In: Berg BO, editor. Principles of Child Neurology. New York: New York, McGraw-Hill, 1996: 1141-1165.

Kakkis ED, Muenzer J, Tiller GE, Waber L, Belmont J, Passage M et al. Enzyme-Replacement Therapy in Mucopolysaccharidosis I. N Engl J Med 2001; 344(3):182-188.

Kreilgaard L, Jones LS, Randolph TW, Frokjaer S, Flink JM, Manning MC et al. Effect of Tween 20 on Freeze-Thawing- and Agitation-Induced Aggregation of Recombinant Human Factor XIII. J Pharm Sci 1998; 87(12):1597-1603.

Moskowitz SM, Dlott B, Chuang PD, Newfeld EF. Cloning and Expression of cDNA Encoding the Human Lysosomal Enzyme, a-L-Iduronidase. School of Medicine and Molecular Biology Institute, UCLA 2001;445.

Myerowitz R, Neufeld EF. Maturation of Alpha-L-Iduronidase in Cultured Human Fibroblasts. J Biol Chem 1981; 256(6):3044-3048.

Sando GN, Neufeld EF. Recognition and Receptor-Mediated Uptake of a Lysosomal Enzyme, a-L-Iduronidase, By Cultured Human Fibroblasts. Cell 1977; 12:619-627.

Scott HS, Anson DS, Orsborn AM, Nelson PV, Clements PR, Morris CP et al. Human a—L-Iduronidase: cDNA Isolation and Expression. Proc Natl Acad Sci USA 1991; 88:9695-9699.

Scott HS, Bunge S, Gal A, Clarke LA, Morris CP, Hopwood JJ. Molecular Genetics of Mucopolysaccharidosis Type I: Diagnostic, Clinical and Biological Implications. Hum Mutat 1995; 6:288-302.

Scott HS, Guo XH, Hopwood JJ, Morris CP. Structure and Sequence of the Human Alpha-L-Iduronidase Gene. Genomics 1992; 13(4):1311-1313.

Southern PJ, Berg P. Transformation Of Mammalian Cells to Antibiotic Resistance With a Bacterial Gene Under Control of the SV40 Early Region Promoter. J Mol Appl Genet 1982; 1(4):327-341.

Urlaub G, Chasin LA. Isolation of Chinese Hamster Cell Mutants Deficient in Dihydrofolate Reductase Activity. Proc Natl Acad Sci USA 1980; 77(7):4216-4220.

Zhao KW, Faull KF, Kakkis ED, Neufeld EF. Carbohydrate Structures of Recombinant Human Alpha-L-Iduronidase Secreted by Chinese Hamster Ovary Cells. J Biol Chem 1997; 272(36):22758-22765.